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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
[illegible]	
ART UNIT	PAPER NUMBER
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DATE MAILED: [illegible]

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/398,365	HAVELUND ET AL.	
	Examiner	Art Unit	
	Fariba Ghashghaee	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-102,116 and 123-139* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-102,116 and 123-139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *68-88, 140-145* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is a)☐ approved b)☐ disapproved

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of

1 ☐ Certified copies of the priority documents have been received.

2 ☒ Certified copies of the priority documents have been received in Application No. *08400256*

3 ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

15)☒ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No.

18)☐ Notice of Informal Patent Application (PTO-152)

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 68-88 are drawn to the insulin derivatives with Xaa at position B30 is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys and their pharmaceutical compositions classified in class 530, subclass 303-304.

II. Claims 89-139 are drawn to the insulin derivative with Xaa at position B30 is deleted, with different lipophilic substituents and their pharmaceutical compositions classified in class 530, subclass 303-304.

III. Claims 140-145 are drawn to the insulin derivatives with the ε-amino group of Lys^{B29} is substituted with a lipophilic substituent having at least 10 carbon atoms classified in class 530, subclass 303-304.

The inventions of groups I, II and III are drawn to patentably distinct inventions. The invention in group I involves the insulin derivatives and their pharmaceutical compositions in which Xaa at position B30 is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys. While the invention in group II involves with a different insulin structure in which Xaa at position B30 is deleted and the ε-amino group of Lys^{B29} is substituted with different lipophilic substituents. The invention in group III involves a different insulin in which the

10 carbon atoms. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Groups II and III, and also the search required for group II is not required for group III, therefore restriction for examination purposes as indicated is proper.

ELECTION OF SPECIES

In addition, the invention in group II contains claims drawn to the following patentably distinct species:

Claims 103-122 involves distinct species of claim 89 in regard to different lipophilic substituents for the ε-amino group of Lys^{B29}. Each one of the substituents have different structure and different functional group which requires separate search.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 103-122 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include

are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

During a telephone conversation with Valeta Gregg on January 5,2001 a provisional election was made without traverse to prosecute the invention of group II and for distinct species of claim 89 in regard to different lipophilic substituents, claim 116 was elected. Affirmation of this election must be made by applicant in replying to this Office action. Claims 68-88 and 140-145 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 89-102, 116 and 123-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Lindsay et al.(USPatent No. 3,950,517), MarKussen et al.(US Patent No. 5,008,241), Muranishi et al. (JP 1-254699), Gammeltoft (Phys. Rev. 64(4): 1321-1378, 1984).

Claims 89-102 ,116 and 123-139 are directed to different derivatives of insulin in which four different residues could be modified; and the pharmaceutical composition of these derivatives and the use of such compositions to traet diabetes. These four different residues are amino acids at A21,B3,B1 and Lys^{B29} positions.

Lindsay et al. (US Pat. No. 3,950,517) discloses the acylation of amino groups of insulin (See column 10) including the acylation of the ε-amino group lysine at B29 position on the B chain. Lindsay also discloses the composition of insulin complexed to Zinc ions (See column 6).Furthermore, Lindsay discloses the method of treating diabetes with the acylated insulin and the pharmaceutical compositions of the acylated insulin (See columns 11 and 12).

The claims differ from Liondsay et al. in the recitation of insulin analogs that substitute the A21 and B3 with different amino acids to increase the stability of the insulin compositions.

Markussen et al. (US Pat. No. 5,008,241) discloses the analogs of insulin by substituting A21 with different amino acid to improve the stability of the insulin at acidic PH levels (See abstract). Markussen also discloses the use of the combination of fast acting, soluble insulin with prolonged acting, crystaline form of insulin in the same injection. In addition, Markussen discloses the inclusion of Zinc in his insulin preparation (See column 8). Finally, Markussen discloses the pharmaceutical compositions of insulin derivatives with Zinc ions at a PH value of 7 (See claim 10).

Claims 89-102,116,123-139 are directed to the insulin derivatives wherein A21 and B3 are any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys and the e-amino group of B29 has a lipophilic substituent which comprises at least 6 carbon atoms. Also includes lipophilic substituents with 12 to 24 carbon atoms. All of this limitations are met by the insulin derivatives prepared by Muranishi and Kiso. Muranishi discloses that an insulin is a composition wherein a fatty acid is bounded to the amino group of amino acids B1 and B29 of the insulin B chain. A fatty acid meets the limitations described earlier.

Gammeltoft teaches that amino acids B28-B30 are not necessary for biological activity (See Pg. 1351, paragraph 4). Gammeltoft also teaches that modifications of the B1 residue do not alter the biological character of the insulin (Pg. 1327, line 9)

Therefore, the deletion of B30 and B1 from the insulin derivative of Lindsay et al. would not make a patentable improvement over the prior art because it was previously known that this modifications would not improve the biological activity of the molecule.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to acylate the insulin of Lindsay et al. in the manner taught by Muranishi and Kiso ,Markussen and Gammeltoft in order to make the insulin products more water soluble.

The person of ordinary skill in the art would have been motivated to make these more water soluble insulin products, and would have been expected reasonable level of success because Muranishi and Markussen et al. taught that the substitution of these water soluble lipophlic substituents increase stability, solubility, and prolonged activity of insulin at neutral PH .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fariba Ghashghaee whose telephone number is (703)305-3586. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr can be reached on (703)308-2454. The fax phone numbers for the organization where this application or proceeding is assigned are (703)305-3014 for regular communications and (703)305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308

FGK

Fariba Ghashghaee
January 16, 2001

SCOTT W. HOUTTEMAN
PRIMARY EXAMINER